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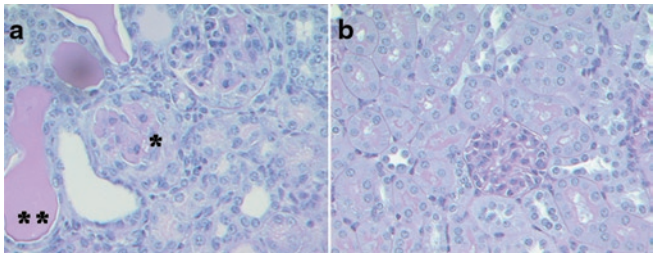
Mannose receptor is critical for the development of crescentic glomerulonephritis

Chavele *et al.*, *J Clin Invest* 2010; **120**: 1469–1478; doi:10.1172/JCI41560



Chavele *et al.*/*J Clin Invest*

Nephrotoxic nephritis in wild-type (WT) (**a**) and $Mr^{-/-}$ (**b**) mice. Sections stained with periodic acid-Schiff demonstrated CGN (single asterisk) and severe tubulointerstitial injury (double asterisk) with dilated tubules and cast formation.

Crescentic glomerulonephritis (CGN) is frequently associated with systemic vasculitis or systemic lupus erythematosus and, despite immunosuppression therapy, often leads to end-stage renal disease. Multiple components of the immune system, including antibodies, complement, and infiltrating lymphocytes, appear to participate in its pathogenesis, but macrophages are an absolute requirement for its development. In response to chemokines produced after cell-mediated immune reactions or antibody deposition, macrophages migrate to and localize in and around the glomerulus, promoting immune injury. Glomerular injury also involves proliferation of mesangial cells, and it is likely that interaction between resident and infiltrating cells is bidirectional, with mesangial cells influencing the response of infiltrating macrophages. The mannose receptor (MR) is a pattern recognition receptor expressed by tissue macrophages, mesangial cells, and some endothelial and dendritic cells. It is a lectin scavenger receptor, important in clearance of microbial and endogenous molecules produced during inflammation and autoantigens implicated in systemic vasculitis, anti-glomerular basement membrane disease, and CGN. In addition, MR binding may enhance Fc-mediated responses, an interesting action since it was recently shown that Fc-mediated responses were critical in induction of CGN. In a recent publication, Chavele *et al.* used the mouse model of nephrotoxic nephritis to investigate the role of the MR in CGN. They induced nephritis in wild-type (WT) mice and in mice with deletion of the MR ($Mr^{-/-}$) and found that whereas the former developed renal dysfunction, proteinuria, CGN, and severe tubulointerstitial inflammation, $Mr^{-/-}$ mice were protected, with preserved renal function and only mild glomerular hypercellularity (Figure). Interestingly, although $Mr^{-/-}$ mice were protected from CGN, they generated humoral and T-cell responses similar to those of WT mice. However, the mice had decreased macrophage and mesangial-cell Fc receptor-mediated functions, including phagocytosis and Fc-mediated oxygen burst activity. In addition, $Mr^{-/-}$ mesangial cells had increased apoptosis, and macrophage interaction with apoptotic mesangial cells induced a non-inflammatory phenotype. These results demonstrate that the MR augments Fc-mediated function and promotes mesangial-cell survival and suggest that targeting the MR may provide an alternative therapeutic approach in CGN.

Juan Oliver

Effects of intensive blood pressure control in type 2 diabetes mellitus

ACCORD Study Group, *N Engl J Med* 2010; **362**: 1575–1585; doi:10.1056/NEJMoa1001286

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study randomized 4733 participants with type 2 diabetes mellitus to one of two different blood pressure targets to determine whether more intensive control of hypertension reduces major cardiovascular events. Intensive therapy targeted a systolic blood pressure of less than 120 mm Hg, and standard therapy a systolic pressure of less than 140 mm Hg. The study noted the effect of treatment target on the composite outcomes of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes over the mean follow-up of 4.7 years and excluded patients with a serum creatinine level of more than 1.5 mg/dl. The treatment strategy focused on the goal blood pressure rather than a comparison of any particular medications or treatment regimens. Randomized participants had a hemoglobin A1c level of 8.3%, a baseline blood pressure of 139.2/76.0 mm Hg, and an estimated glomerular filtration rate (eGFR) of 91.6 ml/min overall at baseline. The study found no differences between treatment groups in the composite primary outcome. The subjects in the intensive-therapy group experienced a lower risk of fatal or nonfatal stroke (hazard ratio, 0.59 and 0.63) with no differences in any other prespecified outcomes. Small, but statistically great, numbers of participants in the intensive-therapy group experienced some potentially blood pressure-related adverse events during follow-up. Seventeen patients in this group experienced hypotension, compared with one in the standard-therapy group. Twelve versus three patients experienced an arrhythmia, nine versus one experienced hyperkalemia, and 99 versus 52 experienced a fall in eGFR to less than 30 ml/min. The median urine albumin-to-creatinine ratio was lower in the intensive-therapy group (12.6 versus 14.9), and fewer participants experienced macroalbuminuria in the intensive-therapy group (6.6 versus 8.1%).

While this study was not designed to examine whether intensive control of blood pressure affects cardiovascular outcomes in chronic kidney disease (CKD) patients per se, it should be recognized that, in patients with normal or near-normal kidney function, a lower blood pressure target does not confer a particular benefit. Until additional information is available, and while ongoing studies address whether cardiovascular or renal outcomes benefit from a lower blood pressure target among patients with CKD, we must utilize this information, as well as conclusions from the African American Study of Kidney Disease and Hypertension

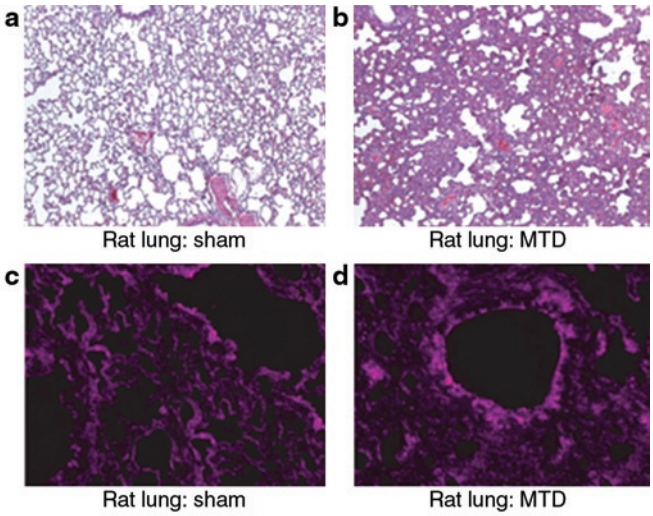
(AASK) trial,[1] in the treatment of patients with normal kidney function to balance an unknown benefit against the potential for a small but increased risk.

Lynda Szczech

[1] *JAMA* 2002; **288**: 2421–2431.

Circulating mitochondrial DAMPs cause inflammatory responses to injury

Zhang *et al.*, *Nature* 2010; **464**: 104–107; doi:10.1038/nature08780



Rats given intravenous mitochondrial DAMPs (MTD) equivalent to mitochondria from a 5% liver injury exhibit marked evidence of lung injury, as shown by hematoxylin and eosin histology (**a**, **b**) and 4-hydroxy-2-nonenal stain for oxidant injury (**c**, **d**).

A systemic inflammatory response syndrome (SIRS) is observed in a number of clinical situations involving serious tissue injury. Clinically, the presentation of SIRS closely resembles sepsis, including frequent acute deterioration of renal function, yet there is no evidence for infection in SIRS. Therefore, investigators have looked for triggers of the inflammatory response but have not identified any clear candidates so far. In sepsis, microbial pathogen-associated molecular patterns (PAMPs) activate innate immunocytes through pattern recognition receptors, thereby initiating the inflammatory response. Similarly, cellular injury can release endogenous 'damage'-associated molecular patterns (DAMPs) that activate innate immunity. Zhang *et al.* reasoned that mitochondria are evolutionary endosymbionts that were derived from bacteria and so might bear bacterial molecular pattern motifs. Such mitochondrial molecules would be released upon tissue damage and could be recognized by receptors of the innate immune system, resulting in a pattern of systemic immune response comparable to bacterial sepsis. The authors demonstrated that injury releases mitochondrial DAMPs into the circulation with functionally important immune consequences. The mitochondrial molecules released include formyl peptides and mitochondrial DNA. These activate human polymorphonuclear neutrophils (PMNs) through formyl peptide receptor-1 and Toll-like receptor 9 (TLR9), respectively. The mitochondrial DAMPs promote PMN Ca^{2+} flux and phosphorylation of mitogen-activated protein kinases, thus leading to PMN migration and degranulation, *in vitro* and *in vivo*. The authors also established that circulating mitochondrial DAMPs can elicit neutrophil-mediated multiple organ injury *in vivo*, thus mimicking SIRS. On the basis of these observations, the authors proposed that cellular disruption by trauma releases mitochondrial DAMPs with evolutionarily conserved similarities to bacterial PAMPs. In the circulation, these signal through innate immune pathways identical to those activated in sepsis, to create a sepsis-like state. The release of such mitochondrial 'enemies within' by cellular injury may be a key link between trauma, inflammation, and SIRS and, as such, may also contribute to the renal involvement in SIRS.

Detlef Schlöndorff

A $CD8^+$ T cell transcription signature predicts prognosis in autoimmune disease

McKinney *et al.*, *Nat Med* 2010; **16**: 586–591; doi:10.1038/nm.2130

Despite its many complications, immunosuppressive therapy is the norm for patients with severe autoimmune diseases. In patients with cancer, gene expression-based biomarkers are starting to facilitate individual tailoring of chemotherapy, thereby decreasing the use of unneeded drugs and the incidence of complications. To examine whether a similar approach could allow individual tailoring of immunosuppressive therapy, McKinney *et al.* performed a transcription profile of purified $CD8^+$ T cells and found that it identified two distinct subject subgroups predicting long-term prognosis in two autoimmune diseases that frequently affect the kidney: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and systemic lupus erythematosus (SLE). Despite the differences between these two diseases, there was a clear correlation between the specific groups and relapsing episodes of disease in both patients with ANCA-associated vasculitis and patients with SLE. The researchers found that the subset of genes defining the poor prognostic group was enriched for genes involved in the interleukin-7 receptor pathway and T-cell receptor signaling and those expressed by memory T cells. Moreover, the poor prognostic group was associated with an expanded $CD8^+$ T cell memory population. Interestingly, they also identified these subgroups in a population of normal subjects. Of potentially great practical importance was that detailed analysis of their data revealed that the subgroups could be identified by measurement of expression of only three genes (*ITGA2*, *NOTCH1*, and *PTPN22*, which encode integrin α2, notch homolog 1, and protein tyrosine phosphatase non-receptor type 2, respectively). This exciting study suggests that transcription profiling of $CD8^+$ T cells may allow use of immunosuppressive therapy in the group of patients who truly need it, sparing patients at low risk of relapse the complications associated with such therapy.

Juan Oliver